Bone 85 (2016) 81–90

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

Inflammatory mediators in osteoarthritis: A critical review of the state-of-the-art, current prospects, and future challenges

Maryam Rahmati [a], Ali Mobasheri [b,c,d], Masoud Mozafari [a,*]

[a] Bioengineering Research Group, Nanotechnology and Advanced Materials Department, Materials and Energy Research Center (MERC), P.O. Box 14155-4777, Tehran, Iran
[b] The D-BOARD European Consortium for Biomarker Discovery, The APPROACH Innovative Medicines Initiative (IMI) Consortium, School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK
[c] Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Arthritis Research UK Pain Centre, Medical Research Council and Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK
[d] Center of Excellence in Genomic Medicine Research (CEGMR), King Fahd Medical Research Center (KFMRC), King AbdulAziz University, Jeddah 21589, Saudi Arabia

ARTICLE INFO

Article history:
Received 10 October 2015
Revised 12 January 2016
Accepted 22 January 2016
Available online 23 January 2016

Keywords:
Osteoarthritis
Cartilage
Synovium
Synovitis
Inflammatory mediators

ABSTRACT

Osteoarthritis (OA) has traditionally been defined as a prototypical non-inflammatory arthropathy, but today there is compelling evidence to suggest that it has an inflammatory component. Many recent studies have shown the presence of synovitis in a large number of patients with OA and demonstrated a direct association between joint inflammation and the progression of OA. Pro-inflammatory cytokines, reactive oxygen species (ROS), nitric oxide, matrix degrading enzymes and biomechanical stress are major factors responsible for the progression of OA in synovial joints. The aim of this review is to discuss the significance of a wide range of implicated inflammatory mediators and their contribution to the progression of OA. We also discuss some of the currently available guidelines, practices, and prospects. In addition, this review argues for new innovation in methodologies and instrumentation for the non-invasive detection of inflammation in OA by modern imaging techniques. We propose that identifying early inflammatory events and targeting these alterations will help to ameliorate the major symptoms such as inflammation and pain in OA patients.

Contents

Abbreviations: LIF, Factor Leukocyte Inhibitory; PGE2, Prostaglandin E2; IL-1Ra, IL-1 receptor antagonist; TIMPs, Tissue Inhibitor of Matrix metalloproteinases; HA, Hyaluronic Acid; hsCRP, High sensitive C-Reactive Protein; IL-1β, Interleukin-1β; NO, Nitric Oxide; mPGES-1, Microsomal PGE Synthase-1; sPLA2, Soluble Phospholipase A2; MMPs, Matrix MetalloProteinases; iNOS or NOS2, Isoform of Nitric Oxide Synthase; RA, Rheumatoid Arthritis; TNF-α, Tumor Necrosis Factor-alpha; MRI, Magnetic Resonance Imaging; PP, Pyrophosphate; US, Ultrasound; JSW, Joint Space Width; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; ACR, American College of Rheumatology; ColX, Type X collagen; C2M, Matrix MetalloProteinase-derived fragments of type II collagen; SF, Synovial Fluid; TKR, Total Knee Replacement; BDNF, Brain-Derived Neurotrophic Factor; TMJ, TemporoMandibular Joint; CTX-I and II, Carboxy Terminal Telopeptides types I and II; COMP, Cartilage Oligomeric Matrix Protein; CTGF, Connective Tissue Growth Factor; FLSs, Fibroblast-Like Synoviocytes; NF, Nuclear Factor; CCL2, C—C motif Ligand 2; ERK1/2, Extracellular Signal-Related Kinase 1/2; BMI, Body Mass Index; HOA, Hand Osteoarthritis; PTX-3, Pentraxin-3; MCV, Modified Citrullinated Vimentin; NC, Control Subjects; PPAR-γ, Peroxisome Proliferator-Activated Receptor-γ; DGAT2, Diacyl Glycerol Acyl Transferase 2; CD36, Cluster of Differentiation; THRSP, Thyroid Hormone Responsive Spot; m-CPPD and t-CPPD, Monoclinic and triclinic Calcium Pyrophosphate Dehydrate; CCL, Cranial Cruciate Ligament; WOMAC, Western Ontario McMaster Universities OA index; SAF-1, Serum Amyloid A-activating Factor 1; CRPM, MMP-mediated breakdown of CRP; C1M, MMP-mediated degradation of type I Collagen; MPO, Myeloperoxidase; HOCl, Hypochlorous acid; Cl_2, Chlorine gas; ECs, Endothelial Cells; CAT, Chloramphenicol Acetyl Transferase; EMSA, Electrophoretic Mobility Shift Assay; COX-1, Cyclooxygenase-1; COX-2, Cyclooxygenase-2; ECM, Extracellular matrix; MNC, Mononuclear cell; OCT, Optical coherence tomography; WAT, White Adipose Tissue; Gd, Gadolinium; CE-US, Contrast-enhanced ultrasound; PAMPs, Pathogen-associated molecular patterns; PRRs, Pattern recognition receptors; TLRs, Toll-like receptors; MAC, Membrane attack complex; ADAMTS, A Disintegrin And Metalloproteinase with ThromboSpondin motifs; NOD, Nucleotide oligomerization domain; NLRs, NOD-like receptors.

* Corresponding author. Tel.: +98 (912) 6490679; fax: +98 (263) 6280033x477.
E-mail address: mozafari.masoud@gmail.com (M. Mozafari).

http://dx.doi.org/10.1016/j.bone.2016.01.019
8756-3282/

1. Introduction

Osteoarthritis (OA) is among the most common joint diseases in the world and a major cause of disability in the aging population [1]. It has been reported that more than 27 million of the US adult population are affected by OA, which is the leading cause of life-years lost to disability in most cases [2]. The disease also affects juveniles, young athletes, many middle-aged people and particularly in older people it can cause severe pain and physical disability [3]. OA is one the major reasons for hip and knee replacement surgeries [4]. Moreover, it most commonly affects the knees, hands, feet, the hips, and the spine. In synovial joints the entire joint is affected, including cartilage, synovial membrane, subchondral bone, ligaments and peri-articular musculature [5,6]. There are a number of major factors affecting the degree of risk for developing OA. These include joint location, obesity, genetic predisposition, joint malalignment, trauma, gender, muscle weakness, physical activity/inactivity, race, bone density, estrogen levels and nutritional status [3,7]. OA is traditionally described as a prototypical non-inflammatory arthropathy but today it is generally accepted that it is an inflammatory disease [8]. Recent studies have provided a much clearer understanding of the role of inflammation in OA, suggesting that inflammation contributes to the symptoms and the progression of OA [9,10]. The most common clinical symptoms are joint pain related to use, pain on movement with a restricted range, cracking of joints (crepitus) and short-lasting inactivity stiffness of joints [9,11]. It has been shown that the inflammatory changes in OA synovium usually take place in the synovial lining with an increased number of inflammatory cells (macrophages) [12,13]. The advanced stages of the disease are visible on plain radiographs, as indicated by narrowing of the joint space (due to cartilage loss), development of osteophytes, and sometimes changes in the subchondral bone [14]. Moreover, a number of ongoing studies have reported the observation of symptoms responsible for the progression of the risk of this disease by arthroscopy, magnetic resonance imaging (MRI), ultrasound (US) and optical coherence tomography (OCT) [15]. Fig. 1 shows a MRI image of a patient in advanced stages of osteoarthritis, and a detailed schematic on the major inflammatory mediators involving in this disease.

In this review, we systematically summarize the role of major inflammatory mediators in the pathophysiology of OA by focusing mainly on pro-inflammatory cytokines (i.e. IL-1α, interleukin-1β (IL-1β), IL-15, IL-17, tumor necrosis factor-alpha (TNF-α)), nitric oxide (NO) and matrix metalloproteinases (MMPs), due to their involvement in this disease. We also discuss the contribution of joint cells, particularly chondrocytes, synoviocytes and inflammatory macrophages to the pathogenesis of OA. The overarching aim of the review is to emphasize the importance of developing new and sensitive methods and diagnostic instruments for the early detection of inflammation in OA by modern imaging techniques. Finally, we put forward a strong argument for developing treatments for decreasing the major symptoms such as inflammation and pain in OA patients.

2. Synovitis in OA

During the last few years, the association between OA progression, symptoms of inflammation, and disease activity has been the subject of a large number of basic and clinical studies [14,16]. A variety of studies have recently demonstrated an important link between OA inflammation and progression of structural changes [9]. In his groundbreaking contribution to OA-related public health George Ehrlich emphasized the importance of inflammation as a component of OA [17]. In a paper published in 1975, Ehrlich described a cohort of predominantly menopausal females who presented with a deforming and

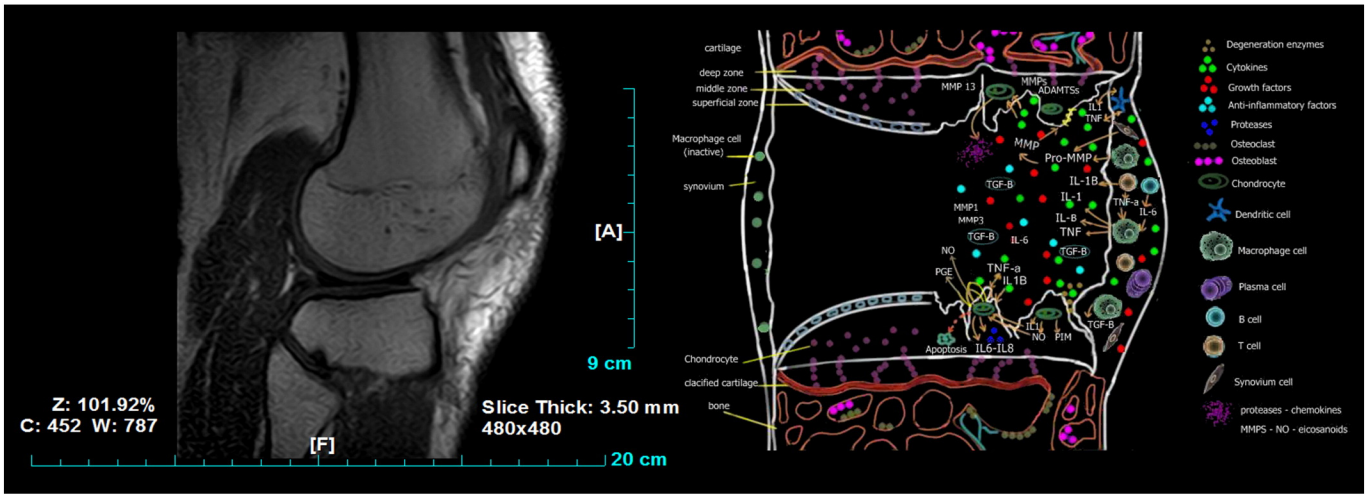

Fig. 1. A MRI image of a patient in advanced stages of osteoarthritis, and a detailed schematic on the major inflammatory mediators involving in this disease.